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Recognition of monoclonal proteins

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INTRODUCTION — The monoclonal gammopathies (paraproteinemias or dysproteinemias) are a group of disorders characterized by the proliferation of a single clone of plasma cells, which produces an immunologically homogeneous protein commonly referred to as a paraprotein or monoclonal protein (M-protein, where the "M" stands for monoclonal). (See ['Definition of an M-protein'](#) below.)

A complete immunoglobulin consists of two heavy polypeptide chains of the same class designated by a capital letter and a corresponding Greek letter:

- Gamma in IgG
- Alpha in IgA
- Mu in IgM
- Delta in IgD
- Epsilon in IgE

The heavy polypeptide chains are further subdivided: IgG has four subclasses (IgG1, IgG2, IgG3, and IgG4) and IgA has two (IgA1 and IgA2). To form the intact immunoglobulin, the paired heavy chains are associated with two light chains of the same type, either kappa or lambda, but not both. (See ["Structure of immunoglobulins"](#).)

Analysis of serum or urine to detect the presence of an M-protein and identify it according to its heavy chain class and light chain type requires a sensitive, rapid, and dependable screening method [[1](#)]. This review will present an overview of the methodologies currently available for these purposes. Discussions of monoclonal gammopathies and the diagnosis of multiple myeloma are presented separately. (See ["Diagnosis of monoclonal gammopathy of undetermined significance"](#) and ["Clinical features, laboratory manifestations, and diagnosis of multiple myeloma"](#).)

DEFINITION OF AN M-PROTEIN — An M-protein (paraprotein, monoclonal protein, M-component) is a monoclonal immunoglobulin secreted by an abnormally

expanded clone of plasma cells in an amount that can be detected by immunofixation of serum and/or urine, or rarely in other body fluids (eg, jejunal fluid in alpha heavy chain disease) [2].

The M-protein can be an intact immunoglobulin (ie, containing both heavy and light chains), can be composed of only light chains (ie, light chain myeloma, light chain deposition disease, AL (light chain) amyloidosis), or rarely can consist of heavy chains only (ie, heavy chain disease, heavy chain deposition disease). (See ["Pathogenesis and clinical features of AL \(primary\) amyloidosis and light and heavy chain deposition diseases"](#) and ["The heavy chain diseases"](#).)

CLINICAL RELEVANCE

Clonal size — The presence of a monoclonal protein in the serum or urine indicates an underlying clonal plasma cell or lymphoproliferative disorder ([table 1](#)). In some cases, the monoclonal protein is the result of an underlying malignancy and is associated with evidence of disease infiltrating lymph nodes, liver, spleen, bone, or other organs (eg, multiple myeloma, solitary plasmacytoma, Waldenstrom's macroglobulinemia). In other cases, the monoclonal protein is the result of a small limited clonal expansion, and causes no symptoms (eg, monoclonal gammopathy of undetermined significance, MGUS). (See ["Diagnosis of monoclonal gammopathy of undetermined significance"](#).)

However, even when the clonal expansion is limited, the monoclonal protein may lead to disabling or fatal disease through one or more of its adverse properties, such as [3]:

- Ability to agglutinate red cells (eg, cold agglutinin disease)
- Insolubility at low temperatures (eg, cryoglobulinemia)
- Increased viscosity (eg, Waldenstrom macroglobulinemia)
- Deposition in tissues with resulting organ dysfunction (eg, AL (light chain) amyloidosis or the immunoglobulin deposition diseases)
- Neuropathy (paraneoplastic neuropathy; eg, MGUS, Waldenstrom macroglobulinemia, primary amyloid, POEMS syndrome).

Accordingly, monoclonal proteins may be part of an asymptomatic limited clonal expansion of plasma cells (eg, MGUS), be a manifestation of a malignancy (eg, myeloma, macroglobulinemia), or may lead to life-threatening complications even if the clonal expansion that produced the M protein is limited (eg, primary amyloidosis). The clinician seeing a patient with a monoclonal protein must therefore make the appropriate diagnosis ([table 1](#)) and initiate effective therapy in a timely manner, in order to prevent irreversible organ damage and/or shortening of life [3].

Interference with laboratory tests — The presence of a circulating monoclonal

protein may interfere with one of more laboratory tests performed on liquid-based automated analyzers, either by precipitating during the analysis [4], or by virtue of its specific binding properties [5].

The most common artifacts are a low value for HDL cholesterol, a high value for bilirubin, as well as altered measurement of inorganic phosphate [4,6-9]. Other examples include interference with measurement of LDL cholesterol, C-reactive protein, antistreptolysin-O, creatinine, glucose, urea nitrogen, iron [10], and inorganic calcium.

Re-analysis using a different method or sample dilution can be employed for obtaining accurate measurements [4]. These events may occur in patients whose clinicians are unaware of the presence of an underlying monoclonal protein and might result in the mismanagement of patients with monoclonal gammopathy, especially as regards measurement of HDL and LDL cholesterol and estimation of cardiovascular risk [7,9].

Sia water test — The phenomenon of protein precipitation when plasma or serum is diluted in low ionic strength solutions or water (ie, positive Sia water test) is neither specific nor sensitive for the presence of monoclonal proteins, and has been described in patients with IgG myeloma, Waldenstrom's macroglobulinemia, in sera with a positive rheumatoid factor and IgG/IgM complexes, as well as in patients with diffuse hypergammaglobulinemia (eg, leishmaniasis) [11,12].

ANALYSIS OF SERUM — Analysis of serum for the presence of M-proteins, or for the evaluation of a patient with increased total serum proteins, is classically performed using electrophoretic techniques, supplemented with additional tests for protein quantification and methodologies to determine whether the protein arises from a single clone (ie, monoclonal).

SERUM PROTEIN ELECTROPHORESIS (SPEP) — Serum protein electrophoresis (SPE or SPEP) is an inexpensive and easy to perform screening procedure. Serum protein electrophoresis is usually done by the agarose gel method (agarose gel electrophoresis), or less commonly by the capillary zone electrophoretic method. It is the recommended method for the detection of an M-protein. The resulting M-protein, if found (figure 1), can then be quantitated by means of a densitometer tracing of the gel (figure 1). (See '[Capillary zone electrophoresis](#)' below.)

In the electrophoretic methodologies (agarose or capillary zone), proteins are classified by their final position after electrophoresis is complete into five general regions: albumin, alpha-1, alpha-2, beta, and gamma (figure 1). These regions, which also use a Greek lettering system, do **not** refer to the immunoglobulin class to which an M-protein may belong, and refer only to mobility through the support medium. The various immunoglobulin classes (IgG, IgA, IgM, IgD, and IgE) are

usually of gamma mobility and make up most of the gamma region, but they may also be found in the beta-gamma and beta regions, and may occasionally extend into the alpha-2 globulin area.

Indications — Serum protein electrophoresis is indicated in all patients in whom multiple myeloma, Waldenström's macroglobulinemia, primary amyloidosis, or a related disorder is suspected. The SPEP should always be performed in combination with serum immunofixation in order to determine clonality (see '[Serum immunofixation](#)' below). (See "[Clinical features, laboratory manifestations, and diagnosis of multiple myeloma](#)" and "[Epidemiology, pathogenesis, clinical manifestations and diagnosis of Waldenstrom macroglobulinemia](#)".)

Serum protein electrophoresis should also be considered in any patient with an elevated total serum protein or otherwise unexplained signs and symptoms suggestive of the presence of a plasma cell disorder. These include any one or more of the following [[13](#)]:

- Elevated erythrocyte sedimentation rate or serum viscosity
- Unexplained anemia, back pain, weakness, or fatigue
- Osteopenia, osteolytic lesions, or spontaneous fractures
- Renal insufficiency with a bland urine sediment
- Heavy proteinuria in a patient over age 40
- Hypercalcemia
- Hypergammaglobulinemia
- Immunoglobulin deficiency
- Bence Jones proteinuria
- Unexplained peripheral neuropathy
- Recurrent infections

As an example, the presence of a localized band or spike on SPEP in adults with nephrotic syndrome, refractory heart failure, orthostatic hypotension, peripheral neuropathy, carpal tunnel syndrome, or malabsorption strongly suggests the possibility of primary amyloidosis (AL), and requires confirmation with immunofixation studies. (See "[Diagnosis of primary \(AL\) amyloidosis](#)".)

Monoclonal gammopathy — A monoclonal protein (M-protein) usually presents as a single narrow peak, like a church spire, in the gamma, beta, or alpha-2 region of the densitometer tracing or as a dense, discrete band on the agarose gel ([figure 1](#)). In approximately 5 percent of sera with an M-protein, two M proteins are present (biclonal gammopathy) ([figure 2](#)) [[14](#)].

A monoclonal protein can be present in a number of different disorders, including B-cell and plasma cell proliferations. The most common of these are listed in the table ([table 1](#)).

Polyclonal gammopathy — The presence of a broad-based peak or band, usually of gamma mobility, suggests a **polyclonal** increase in immunoglobulins, most often due to an infectious, inflammatory, or reactive process ([figure 3](#)). In chronic hepatitis, for example, the gamma component may reach 6 or 7 g/dL. Polyclonal gammopathy may on occasion be present without evidence of an underlying process.

In a retrospective cohort study of 148 patients seen at the Mayo Clinic, in whom a polyclonal gamma globulin level ≥ 3.0 g/dL was found, a single associated medical disorder was present in 130. No patient developed myeloma or a clonal plasma cell proliferative disorder. The most common disorders were [[15](#)]:

- Liver disease — 61 percent
- Connective tissue disease — 22 percent
- Chronic infection — 6 percent
- Hematologic disorders — 5 percent
- Non-hematologic malignancy — 3 percent
- Other — 3 percent

Polyclonal gammopathy, along with bone marrow plasmacytosis, is a common finding in HIV-infected patients [[16](#)]. However, these patients also have an increased incidence of clonal plasma cell disorders (eg, MGUS, multiple myeloma, plasmablastic lymphoma) [[17-19](#)]. (See "[Overview of non-AIDS-defining malignancies in HIV infection](#)", section on 'Plasma cell disorders' and "[AIDS-related lymphomas: Epidemiology, risk factors, and pathobiology](#)".)

Hypogammaglobulinemia — Hypogammaglobulinemia (<0.7 g/dL) is characterized by a decrease in size of the gamma mobility component on SPEP, and should be documented by quantitation of serum IgG, IgA, and IgM levels. This condition may be congenital, sex-linked, and/or part of a combined immunodeficiency state [[20](#)]. (See "[Primary humoral immune deficiencies: An overview](#)" and "[Severe combined immunodeficiency \(SCID\): An overview](#)".) It may also be acquired, as in multiple myeloma, primary amyloidosis, chronic lymphocytic leukemia, lymphoma, or the nephrotic syndrome:

- Panhypogammaglobulinemia occurs in about 10 percent of patients with multiple myeloma. Most of these patients have a Bence Jones protein (monoclonal free kappa or lambda light chains) in the urine, but lack intact

immunoglobulins in the serum [[21,22](#)].

- Panhypogammaglobulinemia is seen in approximately 20 percent of patients with primary amyloidosis, often associated with a nephrotic pattern (mainly albumin with nonselective globulin loss) in the urine.

False negative results — A small M-protein may be present even when quantitative immunoglobulin values, beta and gamma mobility components on SPEP, and total serum protein concentrations are all within normal limits. If a clonal plasma cell disorder is suspected, the most sensitive tests to screen for presence of a monoclonal protein are serum and urine immunofixation, and the serum free light chain assay. In addition, the following caveats need to be kept in mind:

- In alpha heavy chain disease (HCD), which occurs in patients with a form of small intestinal lymphoma called immunoproliferative small intestinal disease (IPSID), one never sees a localized band or sharp peak, presumably because of the tendency of these chains to polymerize, or due to their high carbohydrate content [[23-26](#)]. In some patients these proteins can be found in jejunal fluid but not in the serum. (See "[Clinical presentation and diagnosis of primary gastrointestinal lymphomas](#)", section on '[Lymphoma of the small intestine](#)' and "[The heavy chain diseases](#)", section on '[Alpha HCD](#)'.)
- In mu HCD, panhypogammaglobulinemia is a prominent feature and a localized band is found in only 40 percent [[27](#)]. (See "[The heavy chain diseases](#)", section on '[Mu HCD](#)'.)
- In an occasional patient with gamma HCD, the electrophoretic tracing may appear broad and heterogeneous rather than showing a localized band [[25,28,29](#)]. (See "[The heavy chain diseases](#)", section on '[Gamma HCD](#)'.)
- An M-protein may produce a broad band in the agarose gel, suggesting a polyclonal pattern. This can occur when an M-protein complexes with other plasma components, or when there are IgM dimers and pentamers, IgA polymers, or IgG aggregates.
- Some patients make only monoclonal light chains (Bence Jones proteinemia), which are usually present in concentrations too low to be visible as a spike in the agarose gel, because of rapid excretion in the urine [[30](#)]. The serum concentrations will rise if such patients develop renal failure.
- In some patients with IgD myeloma, the M-protein spike may be small and easily overlooked.

False positive results — Serum protein elements other than immunoglobulins may falsely suggest the presence of an M-protein. As examples:

- Fibrinogen (in plasma) is seen as a discrete band between the beta and gamma mobility regions. This is indistinguishable from an M-protein; addition of thrombin to the specimen will produce a clot if fibrinogen is present. The presence of fibrinogen is established if the discrete band is no longer detected when electrophoresis is repeated after the addition of thrombin.
- Hemoglobin-haptoglobin complexes secondary to hemolysis may appear as a large band in the alpha-2-globulin region.
- High concentrations of transferrin in patients with iron-deficiency anemia may produce a localized band in the beta region.
- Nephrotic syndrome is often associated with increased alpha-2 and beta bands which can be mistaken for an M-protein. Serum albumin and gamma globulin concentrations are usually reduced in this setting.
- Nonspecific increases in acute phase reactants or certain hyperlipoproteinemias may result in increases in alpha-1 bands.
- A common artifact is the presence of a protein band at the point of application of the sample. A clue to the presence of this artifact is the presence of this band on simultaneously performed samples from multiple patients.

Other SPEP patterns — A number of other patterns may be observed on the SPEP:

- A decrease in serum albumin and an increase in alpha-1 and alpha-2 globulins may be present in patients with infection or metastatic malignancy.
- Marked reduction of the alpha-1 globulin component is usually due to a deficiency of alpha-1 antitrypsin.
- Two albumin bands (bisalbuminemia) may be found. This familial abnormality produces no symptoms [\[31\]](#).

SERUM IMMUNOFIXATION — Serum protein electrophoresis is a useful screening procedure, although, as noted above, an M-protein may be easily overlooked or an apparent M-protein may actually represent a polyclonal increase in immunoglobulins or a nonimmunoglobulin. Consequently, the laboratory must perform additional studies, usually serum immunofixation, in order to ascertain the presence of an M-protein and to determine its type. (See ["Function and clinical applications of immunoglobulins"](#).)

Serum immunofixation is critical for the differentiation of a monoclonal from a polyclonal increase in immunoglobulins. This technique may be performed using

commercial kits or laboratory personnel can pour their own plates and cut the appropriate troughs.

In immunofixation, the patient's serum is electrophoresed into at least five separate lanes. Following electrophoretic separation of the serum proteins, each sample is overlaid with a different monospecific antibody, usually three for the heavy chain component and two for the light chain component (eg, anti-gamma, anti-mu, anti-alpha, anti-kappa, and anti-lambda, respectively). Precipitation of proteins (ie, the antigen-antibody complex) is allowed to occur, followed by washing (nonprecipitated proteins wash out) and staining of the remaining immunoprecipitates.

An M-protein is characterized on immunofixation by the combined presence of a sharp, well-defined band associated with a single heavy-chain class and a sharp and well-defined band with similar mobility characteristics which reacts with either kappa or lambda light chain antisera, but not both ([figure 4](#)).

Indications — Serum immunofixation is more sensitive than serum protein electrophoresis, and also determines the heavy and light chain type of the monoclonal protein. However, unlike serum protein electrophoresis, immunofixation does not give an estimate of the size of the M protein (ie, its serum concentration), and thus should be done in conjunction with electrophoresis. Serum immunofixation should be performed when a **sharp** band or peak is found in the agarose gel (ie, a monoclonal protein on SPEP) or when multiple myeloma, macroglobulinemia, primary amyloidosis, solitary or extramedullary plasmacytoma, or a related disorder is suspected, despite a normal serum protein electrophoresis pattern [[3](#)].

Immunofixation will detect a serum M-protein at a concentration of at least 0.02 g/dL and a urine M-protein at a concentration of ≥ 0.004 g/dL [[13](#)]. It should always be performed in the presence of otherwise unexplained sensory motor peripheral neuropathy, nephrotic syndrome, refractory heart failure, orthostatic hypotension, carpal tunnel syndrome, malabsorption, or whenever the clinical situation suggests the possibility of primary amyloidosis (AL). (See "[Diagnosis of primary \(AL\) amyloidosis](#)".)

There are also a variety of other indications for immunofixation:

- Detection of a small M-protein in the presence of normal or increased background immunoglobulins.
- In patients with multiple myeloma or macroglobulinemia in whom treatment has resulted in disappearance of the band on routine electrophoresis.
- Recognition and distinction of biclonal (two M-proteins) ([figure 5](#)) or triclonal

(three M-proteins) ([figure 6](#)) gammopathies [[32](#)]. Such multiple M-proteins may have only a single band or spike on SPEP, and may otherwise be missed.

In addition, the possibility of IgD and IgE monoclonal proteins must be excluded by immunofixation using IgD and IgE antisera in all patients with a monoclonal light chain in the serum but no reactivity to anti-G, anti-M, or anti-A.

When following patients with multiple myeloma, MGUS, or a related disorder, once the presence of a monoclonal protein and its type are initially confirmed by immunofixation, it is not necessary to repeat immunofixation unless needed to document complete response to therapy. Patients can usually be followed with electrophoresis of serum (SPEP) or urine (UPEP) proteins.

Biclonal gammopathy — A biclonal gammopathy is suspected when there are two proteins with different mobilities comprising two different monoclonal heavy chains with their respective monoclonal light chains ([figure 5](#)) [[33](#)]. A biclonal gammopathy may also consist of two heavy chains of the same class and monoclonal light chains of the same type. In this setting, one must be careful to exclude monomers and aggregates as well as monomers and polymers of an M-protein. As an example, if two IgA spikes having the same class light chain are present, the two components should be considered parts of the same abnormal clone, since they most likely represent a monomer and polymer, respectively, of a single protein. Similarly, IgM pentamers (19S IgM) and monomers (7S IgM) may appear as two distinct bands on immunofixation.

Two bands may also be seen in the presence of monomers and aggregates of IgG. As a general rule, if both bands migrate toward the cathode or anode, it is likely that a monoclonal protein (with monomers, polymers, or aggregates) is present; biclonal gammopathy is almost certain when one of the bands migrates toward the anode and the other band migrates toward the cathode.

Patients with biclonal gammopathy of undetermined significance have the same clinical spectrum as those with monoclonal gammopathy of undetermined significance (MGUS), and should be followed in the same manner.

QUANTITATION OF IMMUNOGLOBULINS — Quantitation of immunoglobulins is the most useful technique for the detection of hypogammaglobulinemia. The use of a rate nephelometer is a good method for this purpose. The degree of turbidity produced by antigen-antibody interaction is measured by nephelometry in the near ultraviolet regions. Because the method is not affected by the molecular size of the antigen, the nephelometric technique accurately measures 7S IgM, polymers of IgA, or aggregates of IgG.

Estimation of quantitative immunoglobulins by nephelometry does not allow an assessment of monoclonality. Increased levels can be due to polyclonal or

monoclonal elevations; clonality needs to be established using SPEP and immunofixation, as discussed above.

Although the reason is not well understood, nephelometric levels of IgM are often 1000 to 2000 mg/dL greater than expected on the basis of the SPEP densitometry tracing [34]. Because of the overestimation of IgM by nephelometry, it has been recommended that serum protein electrophoresis followed by densitometry is preferable, the results of which usually more closely agree with the clinical presentation [35]. IgG and IgA may also be spuriously increased using nephelometry.

Quantitation of immunoglobulins using nephelometry is a useful adjunct to the SPEP and UPEP in following patients with multiple myeloma specifically to assess response to therapy. However, when assessing response, SPEP values should only be compared to SPEP values, and quantitative immunoglobulin values only to quantitative immunoglobulin values.

In certain situations quantitative immunoglobulin values may be more reliable than the SPEP:

- Small beta-migrating M-proteins (usually IgA M-proteins) are contaminated by normal immunoglobulins that are often greater in quantity than the M spike itself.
- When the M-spike is so large (>4 g/dL) and narrow on agarose that the SPEP underestimates the actual immunoglobulin level (by more than 1.5 g/dL), due to technical staining properties of the agarose gel.

Quantitation of immunoglobulins can also be performed with radial immunodiffusion. However, this method, which is standardized with 19S IgM and 7S IgA, often gives a spuriously high IgM value because of the presence of 7S IgM and a spuriously low IgA level because of polymers of the IgA monoclonal proteins. Thus, radial immunodiffusion is not recommended for immunoglobulin quantitation.

CAPILLARY ZONE ELECTROPHORESIS — Capillary zone electrophoresis refers to an alternative method of performing serum protein electrophoresis compared to the agarose gel technique. It measures protein on-line via light absorbance techniques; protein stains are not necessary and no point of application is seen [36,37]. The electrophoretograms are similar to those seen with high resolution agarose gel serum protein electrophoresis.

Capillary electrophoresis appears to be slightly more sensitive than agarose gel electrophoresis.

IMMUNOSUBTRACTION — Immunosubtraction is an alternative procedure to

serum immunofixation. In this procedure the serum sample is incubated with Sepharose beads coupled with anti-gamma, -alpha, -mu, -kappa, and -lambda antisera. After incubation with each of the heavy and light chain antisera, the supernatants are reanalyzed to determine which reagent(s) removed the electrophoretic abnormality. The immunosubtraction procedure is technically less demanding, is automated, and is therefore a useful alternative to serum immunofixation [36,37]. It has the same indications, and accomplishes the same goals, as serum immunofixation.

IMMUNOELECTROPHORESIS — Immunoelectrophoresis may also be used for the detection of an M-protein. This technique differs from immunofixation in that the end-point is a precipitin arc rather than a distinct band. Most laboratories no longer perform immunoelectrophoresis and rely instead on immunofixation techniques.

SERUM VISCOSITY — Serum viscosity should be performed in any patient with a monoclonal gammopathy and signs and symptoms suggesting the hyperviscosity syndrome. These symptoms include: oronasal bleeding, blurred vision, dilatation of retinal veins, flame-shaped retinal hemorrhages, unexplained heart failure, or neurologic symptoms such as headaches, vertigo, nystagmus, deafness, ataxia, diplopia, paresthesias, stupor, or somnolence [38].

Waldenström macroglobulinemia, with increased concentrations of IgM, is the most common cause of hyperviscosity, but hyperviscosity can also occur in patients with high concentrations of monoclonal IgA or IgG. (See ["Epidemiology, pathogenesis, clinical manifestations and diagnosis of Waldenstrom macroglobulinemia", section on 'Hyperviscosity syndrome'.](#)) Serum viscosity should be determined whenever the monoclonal IgM protein spike is >4 g/dL or the IgA or IgG protein spike is >6 g/dL.

The Ostwald-100 viscometer is an inexpensive and satisfactory instrument for measurement of viscosity, but a Wells-Brookfield (Brookfield Engineering Laboratory, Stoughton, MA) is preferred because it is more accurate, requires less serum (1.0 mL), and can be performed at different shear rates and at various temperatures. In addition, determinations can be made much more rapidly than with the Ostwald device, especially if the viscosity of the serum is high. Another option is the Sonoclot Coagulation and Platelet Function Analyzer (Sienco, Inc. Wheat Ridge, CO).

The normal value for serum viscosity is 1.5 centipoise (CP), but hyperviscosity symptoms are rarely present unless the viscosity is >4 CP. However, many laboratories report viscosity in relative terms (eg, relative to distilled water or saline). The normal relative viscosity in our laboratory is 1.8. Because of the often poor correlation between viscosity and symptoms, and the fact that relative and absolute (in centipoise, see below) viscosities of plasma are similar, these two units can be used interchangeably.

The relationship between serum viscosity and IgM protein concentration is nonlinear. Thus, with low serum IgM concentrations, an increase of 1 to 2 g/dL produces only a small increase in serum viscosity, but with IgM levels of 4 to 5 g/dL, an increment of 1 to 2 g/dL greatly increases viscosity. In addition, the relationship between serum viscosity and symptoms of hyperviscosity is not precise. Although many patients have symptoms when the viscosity is >4 centipoise (CP), most have symptoms when the viscosity reaches 6 to 7 CP. However, we have also seen higher viscosities in the absence of symptoms or physical findings of the hyperviscosity syndrome.

The specific viscosity level at which clinical symptoms occur is affected not only by the serum protein concentration but also by molecular characteristics of the protein, aggregation of protein molecules, simultaneous presence of diseases involving the microvasculature, hematocrit, and cardiac status. Consequently, clinical evaluation of the patient is important. The decision to perform plasmapheresis should be made on the basis of signs and symptoms of hyperviscosity rather than the viscosity value per se. (See ["Epidemiology, pathogenesis, clinical manifestations and diagnosis of Waldenstrom macroglobulinemia", section on 'Hyperviscosity syndrome' and "Treatment and prognosis of Waldenstrom macroglobulinemia".](#))

It is useful to measure the serum viscosity and to perform SPEP before and after each plasmapheresis to determine effectiveness. Such patients should also be monitored by periodic SPEP. If the serum M-protein values increase or if symptoms or signs of hyperviscosity recur, the serum viscosity should be repeated.

SERUM FREE LIGHT CHAINS — In 16 percent of our patients with multiple myeloma, only a Bence Jones protein (light chain) was produced [22], often in concentrations too low to be detected by routine immunofixation techniques applied to serum samples. Under such circumstances, or when primary systemic amyloidosis or light-chain-deposition disease are suspected, it is routine to analyze a 24-hour urine collection for the presence of free light chains (see ["Analysis of urine"](#) below and ["Clinical features, laboratory manifestations, and diagnosis of multiple myeloma", section on 'Monoclonal proteins'](#)).

Immunoassays are now available for detection of low concentrations of monoclonal free light chains in serum. In this assay, normal levels were as follows (95 percent confidence intervals) [39]:

- Free serum kappa light chains — 3.3 to 19.4 mg/L
- Free serum lambda light chains — 5.7 to 26.3 mg/L
- Ratio of kappa to lambda free light chains — 0.26 to 1.65

This assay has been proven to have value for the diagnosis, prognosis, and

response to treatment in a number of monoclonal plasma cell disorders, including MGUS, AL amyloid, and multiple myeloma [40].

This free light chain assay is more sensitive for the detection of monoclonal free light chains than urine immunofixation. This was illustrated in a study of paired serum and urine samples from patients with multiple myeloma who tested positive for either kappa or lambda monoclonal free light chains in their serum; only 51 and 35 percent, respectively, of their paired urine samples were positive for Bence Jones protein on urine immunofixation [41].

When this assay was applied to sera from patients previously diagnosed as having nonsecretory myeloma, the improved sensitivity allowed 19 of 28 to be reclassified as secretory light chain myeloma (figure 7) [42,43]. (See "[Clinical features, laboratory manifestations, and diagnosis of multiple myeloma](#)", section on '[Non-secretory myeloma](#)'.)

Indications and uses — Measurement of free light chains is useful in a number of settings, such as:

- Diagnosis and monitoring progress of patients with non-secretory myeloma and oligosecretory (<1g/dL monoclonal protein in the serum and <200mg/day monoclonal protein in the urine) myeloma.
- Diagnosis and monitoring progress of patients with light chain myeloma as well as primary systemic amyloidosis, in whom the underlying clonal plasma cell disorder may otherwise be difficult to detect and monitor [44,45].
- Predicting risk of progression of MGUS. (See "[Clinical course and management of monoclonal gammopathy of undetermined significance](#)", section on '[Risk stratification](#)'.)
- Predicting risk of progression of smoldering multiple myeloma. (See "[Clinical features, laboratory manifestations, and diagnosis of multiple myeloma](#)", section on '[Smoldering multiple myeloma](#)'.)
- Predicting risk of progression of solitary plasmacytoma of bone. (See "[Diagnosis and management of solitary plasmacytoma of bone](#)", section on '[Prognosis](#)'.)
- Diagnosis, monitoring during and after treatment, and perhaps prognosis of patients with multiple myeloma and an intact immunoglobulin [46,47].
- Potentially obviating the initial need for urine protein studies in the screening algorithm for monoclonal gammopathies when serum free light chain analysis is performed along with serum protein electrophoresis and serum

immunoelectrophoresis [48]. If a monoclonal protein is found, electrophoresis and immunofixation of an aliquot from a 24-hour urine collection should then be performed.

Use in patients with renal failure — The normally rapid renal clearance of serum free light chains is reduced in the presence of renal failure. As a result, serum free light chain concentrations rise as the glomerular filtration rate falls, and may be 20 to 30 times normal in end-stage renal failure [49]. In addition, the kappa/lambda ratio, which is normally in the range of 0.26 to 1.65, may rise to as high as 3.1 in the presence of renal failure. The change in kappa/lambda ratios with increasing renal impairment is of potential clinical relevance in the following settings:

- Patients might be misclassified as having a kappa monoclonal gammopathy because of an increased kappa/lambda ratio due solely to renal insufficiency.
- Patients with a lambda monoclonal gammopathy along with renal insufficiency might have a relatively normal kappa/lambda ratio and be missed because of the relative increase in kappa chains due to the renal insufficiency.

ANALYSIS OF URINE — A number of methods are available for determination of the amount of protein excreted into the urine and for determining the nature and clonality of these proteins. Although many methods are listed below, the main tests required for the evaluation of monoclonal plasma cell disorders, including multiple myeloma and primary amyloidosis, are urine protein electrophoresis and urine immunofixation.

Dipstick testing — Dipsticks are used in many laboratories to screen for the presence of protein in the urine. The dipstick is impregnated with a buffered indicator dye that binds to protein and produces a color change proportional to the amount of protein bound to it. However, dipsticks are insensitive to the presence of Bence Jones protein (free kappa or lambda light chains) and should **not** be used for this purpose [50,51]. To the contrary, it is the presence of a negative or trace dipstick for protein in a patient over the age of 50 who presents with otherwise unexplained renal failure with a bland urine sediment that should raise suspicion of myeloma kidney. Urinary protein should be measured by other methods in all of these patients. (See "[Types of renal disease in multiple myeloma](#)".)

Other detection methods — Detection of protein in the urine of patients with monoclonal gammopathy can be accomplished with sulfosalicylic acid or Exton's reagent. These agents detect albumin, globulin, Bence Jones protein, polypeptides and proteases. False-positive reactions may be induced by penicillin or its derivatives, [tolbutamide](#) metabolites, sulfisoxazole metabolites, and certain organic roentgenographic contrast media [52]. The biuret method is satisfactory for the

quantitation of total protein.

Sulfosalicylic acid test — The SSA test is performed by mixing one part urine supernatant (eg, 2.5 mL) with three parts 3 percent sulfosalicylic acid, and grading the resultant turbidity according to the following schema (the numbers in parentheses represent the approximate protein concentration):

0 = no turbidity (0 mg/dL)

trace = slight turbidity (1 to 10 mg/dL)

1+ = turbidity through which print can be read (15 to 30 mg/dL)

2+ = white cloud without precipitate through which heavy black lines on a white background can be seen (40 to 100 mg/dL)

3+ = white cloud with fine precipitate through which heavy black lines cannot be seen (150 to 350 mg/dL)

4+ = flocculent precipitate (>500 mg/dL).

The combination of a 3+ or 4+ SSA test and a negative or trace dipstick is usually indicative of a nonalbumin protein in the urine. In the adult over age 50, this is most often a monoclonal light chain. Further testing is required for confirmation.

Heat test for light chains — Monoclonal light chains in the urine characteristically precipitate at 40 to 60°C, dissolve at 100°C, and reprecipitate on cooling to between 40 and 60°C [53]. However, the heat test may give a false positive result. In this setting, a broad-based gamma-mobility band and normal appearing kappa and lambda bands are seen on immunofixation. Presumably, the false positive result is due to an excess of polyclonal light chains, which occurs most often in patients with renal insufficiency [54]. False negative tests also may be seen.

For these reasons, the heat test is not recommended for the detection of Bence Jones proteins. Immunofixation of an adequately concentrated urine specimen is the recommended test.

24-HOUR URINE PROTEIN ELECTROPHORESIS (UPEP) — The urine protein electrophoresis is analogous to the serum protein electrophoresis (SPEP), and is used to detect monoclonal (M) proteins in the urine by an electrophoretic method.

A 24-hour urine collection is necessary for determination of the total amount of protein excreted in the urine per day. The quantity of M-protein excreted is determined by measuring the size (percent) of the M-spike in the densitometer tracing and multiplying it by the total 24-hour urinary protein excretion. The amount of protein can be expressed as mg/dL or mg/L but it is much more useful to report the M-protein in g/24 hours because of wide variability in the daily urinary

volume. The 24-hour urine specimen requires no preservative and may be kept at room temperature during collection.

On UPEP, a urinary M-protein is seen as a dense localized band on agarose or a tall narrow peak on the densitometer tracing ([figure 8](#)). Generally, the amount of urinary monoclonal protein correlates directly with the size of the plasma cell burden, as long as renal function is relatively normal. Consequently, urinary M-protein excretion is useful in determining the response to chemotherapy or progression of disease.

Indications — All patients with a diagnosis of a plasma cell dyscrasia should have a baseline urine protein electrophoresis (and immunofixation) of an aliquot from a 24-hour urine collection. This test is essential to detect the presence of potentially nephrotoxic concentrations of urinary light chains. (See "[Pathogenesis and diagnosis of myeloma cast nephropathy \(myeloma kidney\)](#)".)

Urine electrophoresis testing is subsequently required to detect progression and to monitor response to therapy in patients who have urinary monoclonal proteins at baseline.

Urine protein electrophoresis (and immunofixation) has been used also as a standard screening test for patients in whom there is clinical suspicion for a monoclonal plasma cell proliferative disorder such as myeloma or primary amyloidosis. The serum free light chain assay can be used as an alternative method.

URINE IMMUNOFIXATION — Urine immunofixation is the preferred method for identification of a monoclonal protein in the urine. As in the case of serum immunofixation it is more sensitive than urine electrophoresis, and allows determination of the heavy and light chain type of the urinary monoclonal protein. It does not estimate the size of the monoclonal protein and hence is done in conjunction with urine protein electrophoresis.

The presence of a urinary monoclonal light chain on immunofixation is characterized by a discrete band with reactivity to either kappa or lambda antisera, but not both ([figure 9](#)). Two discrete bands with either kappa or lambda antisera (but not both) may be found; this is usually due to the presence of monomers and dimers of the monoclonal light chain protein. However, a discrete band with heavy chain antisera reactivity corresponding to the type of heavy chain present in the patient's serum and coinciding with one of the two light chain bands indicates the presence of a fragment of the intact immunoglobulin ([figure 10](#)). This is of no particular clinical relevance.

A biclonal gammopathy with one monoclonal protein having a kappa chain and the other having a lambda chain rarely occurs. Occasionally, regularly spaced faint but

discrete multiple bands are seen on immunofixation. These restricted bands represent related polyclonal free light chains and are not to be confused with monoclonal light chains. This phenomenon has been described as "ladder light chain" or a "pseudo-oligoclonal pattern" [55].

If the patient has nephrotic syndrome, the presence of a monoclonal light chain strongly suggests either primary amyloidosis (AL) or light chain deposition disease in almost all instances. If electrophoresis of the urine reveals a localized globulin band and immunofixation does not demonstrate a monoclonal light chain, one should suspect the possibility of heavy chain deposition disease. Immunofixation should then be performed with antisera to IgG (gamma heavy chains). (See ["Diagnosis of primary \(AL\) amyloidosis"](#) and ["Pathogenesis and clinical features of AL \(primary\) amyloidosis and light and heavy chain deposition diseases"](#).)

Theoretically, antisera that recognize only free kappa or free lambda light chains should be used rather than antisera that recognize both free light chains as well as light chains which are part of an intact immunoglobulin. However, such antisera are often either nonspecific or insufficiently potent. In addition, a patient may have an immunoglobulin fragment that free kappa or free lambda antisera do not recognize. Thus, it is advisable to use kappa and lambda antisera that are monospecific and potent and able to recognize both free and combined light chains when performing immunofixation. This is especially important, as some patients have isolated Bence Jones proteinuria with no M-spike in the serum [30,42].

Indications — Urine immunofixation should be performed at baseline in all patients with a diagnosis of a plasma cell dyscrasia. Immunofixation should be performed in these patients even if the routine urine analysis is negative for protein, 24-hour urine protein concentration is within normal limits, and electrophoresis of a concentrated urine specimen shows no globulin peak. Immunofixation is sufficiently sensitive to detect a urine M-protein of ≥ 0.004 g/dL [13]. Urine immunofixation is subsequently required to assess and document complete response in patients receiving therapy.

Urine immunofixation has also been used as a standard screening test for patients in whom there is clinical suspicion for a monoclonal plasma cell proliferative disorder such as myeloma or primary amyloidosis. The serum free light chain assay can be used as an alternative method.

EVALUATION OF MONOCLONAL GAMMOPATHIES — This issue is discussed separately. (See ["Diagnosis of monoclonal gammopathy of undetermined significance"](#), section on 'Summary and recommendations'.)

It is of great importance for the physician to be in contact with the laboratory concerning interpretation of these laboratory tests. It is also essential that the

laboratory know when the physician suspects primary amyloidosis or a plasma cell/lymphocytic disorder so that a greater effort can be made for the detection of an M-protein, which may be present in such a low concentration that it is not be detected by routine serum or urine protein electrophoresis, but may be detected by more sensitive techniques (eg, immunofixation or free light chain assay) [[56,57](#)].

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GRAPHICS

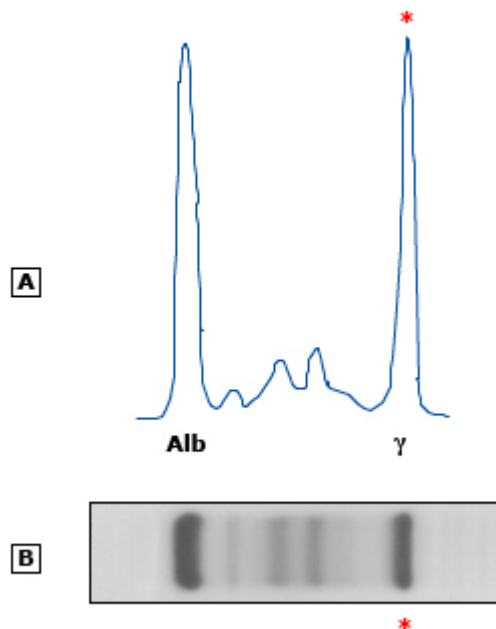
Disorders associated with the presence of a monoclonal gammopathy

Plasma cell disorders
Monoclonal gammopathy of undetermined significance (MGUS)
Biclonal gammopathy of undetermined significance
Idiopathic Bence Jones proteinuria
POEMS syndrome, Osteosclerotic myeloma
Castleman's disease
AL (light chain) amyloidosis, light chain and heavy chain deposition diseases
Solitary plasmacytoma
Multiple myeloma, Smoldering multiple myeloma
B-cell lymphoproliferative disorders
Non-Hodgkin's lymphoma
Chronic lymphocytic leukemia
Lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia)
Post-transplant monoclonal gammopathies
Heavy chain diseases
Connective tissue disorders*
Systemic lupus erythematosus
Rheumatoid arthritis
Sjogren syndrome
Scleroderma
Psoriatic arthritis
(Polymyalgia rheumatica)
Associated with infections*

Hepatitis C virus infection
HIV/AIDS
Dermatologic disorders
Scleredema (scleromyxedema), Lichen myxoedematosus
Diffuse plane xanthomatosis
Urticaria and IgM (Schnitzler's syndrome)
Subcorneal pustular dermatosis
Necrobiotic xanthogranuloma
Pyoderma gangrenosum
Miscellaneous disorders*
Acquired von Willebrand disease
Acquired C1 esterase inhibitor deficiency (angioedema)
Eosinophilic fasciitis
Cryoglobulinemia, cryofibrinogenemia
Myelodysplastic syndrome
Chronic neutrophilic leukemia
Sensorimotor neuropathy with MGUS
Capillary leak syndrome
T-cell large granular lymphocyte leukemia
Cold agglutinin disease

* Some of the disorders listed here may be associated with the presence of an underlying lymphoproliferative disorder.

Monoclonal pattern SPEP



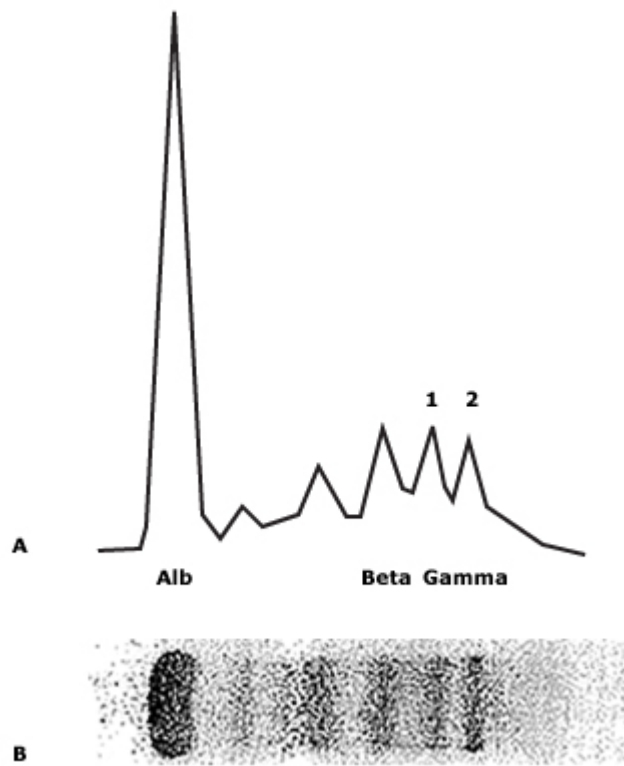
(A) Densitometer tracing of these findings reveals a tall, narrow-based peak (red asterisk) of gamma mobility and has been likened to a church spire. The monoclonal band has a densitometric appearance similar to that of albumin (alb) and a reduction in the normal polyclonal gamma band.

(B) A dense, localized band (red asterisk) representing a monoclonal protein of gamma mobility is seen on serum protein electrophoresis on agarose gel (anode on left).

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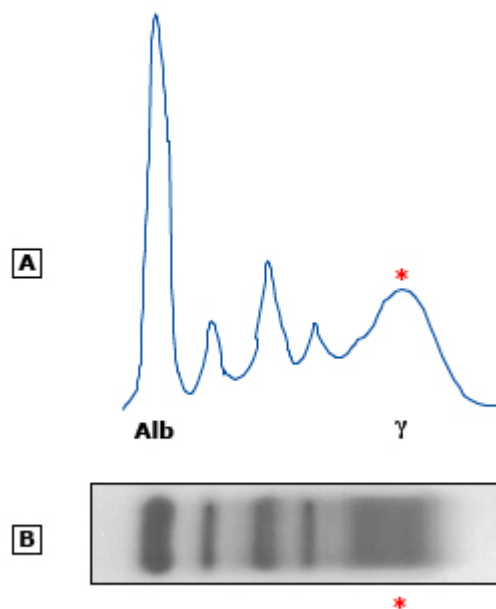
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Biclonal gammopathy



Panel B: A biclonal pattern, with two small, discrete gamma bands, is seen on serum protein electrophoresis on agarose gel (anode on left). Panel A: Densitometer tracing of these findings shows the two protein peaks with gamma mobility.

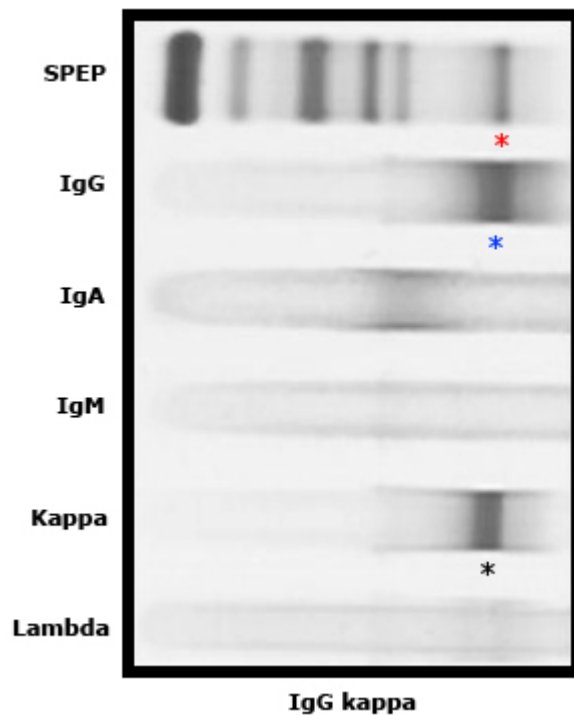
Polyclonal gammopathy



(A) Densitometer tracing of these findings reveals a broad-based peak of gamma mobility. This pattern is most often due to the presence of an inflammatory or reactive process, such as chronic liver disease, connective tissue disease, chronic infection, or a lymphoproliferative disorder.

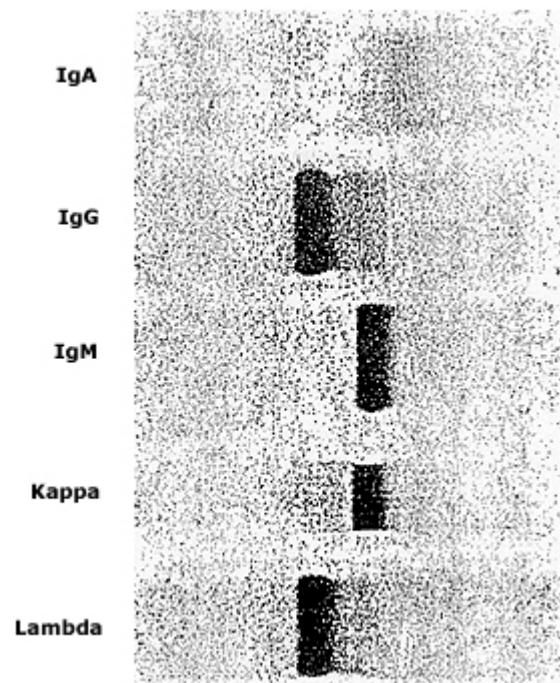
(B) A polyclonal pattern is seen on serum protein electrophoresis on agarose gel (anode on left). The band at the right (red asterisk) is broad, and extends throughout the gamma mobility area. *Reproduced with permission from: Kyle, RA, Rajkumar, SV. Plasma cell disorders. In: Cecil textbook of medicine, 22nd ed, Goldman, L, Ausiello, DA (Eds), WB Saunders, Philadelphia 2004. p.1184. Copyright © 2004 Elsevier.*

Monoclonal gammopathy on immunofixation



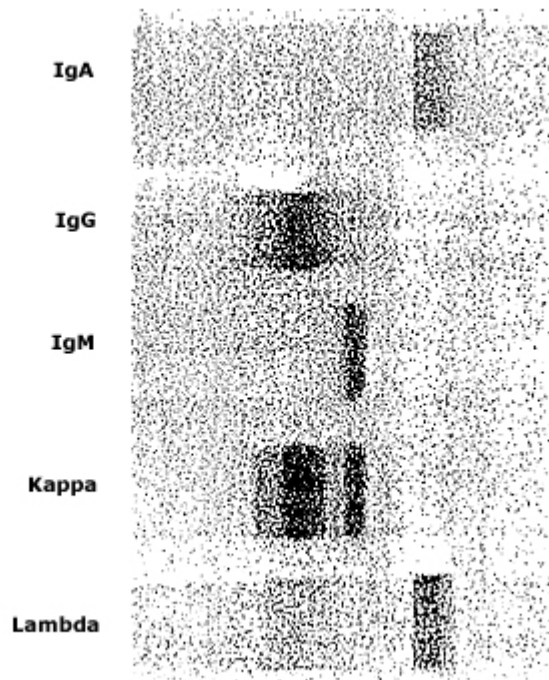
This figure shows the serum protein electrophoretic pattern (SPEP) and immunofixation pattern of a single serum sample with antisera to heavy chain determinants of IgG, IgA, and IgM, and to kappa and lambda light chains. It shows a discrete band on SPEP (red asterisk) and a band with similar mobility reacting only with the antisera to IgG (blue asterisk) and the kappa light chain (black asterisk), indicative of an IgG kappa monoclonal protein. *Reproduced with permission from: Kyle, RA, Rajkumar, SV. Plasma cell disorders. In: Cecil textbook of medicine, 22nd ed, Goldman, L, Ausiello, DA (Eds), WB Saunders, Philadelphia 2004. p.1184. Copyright © 2004 Elsevier.*

Biclonal gammopathy



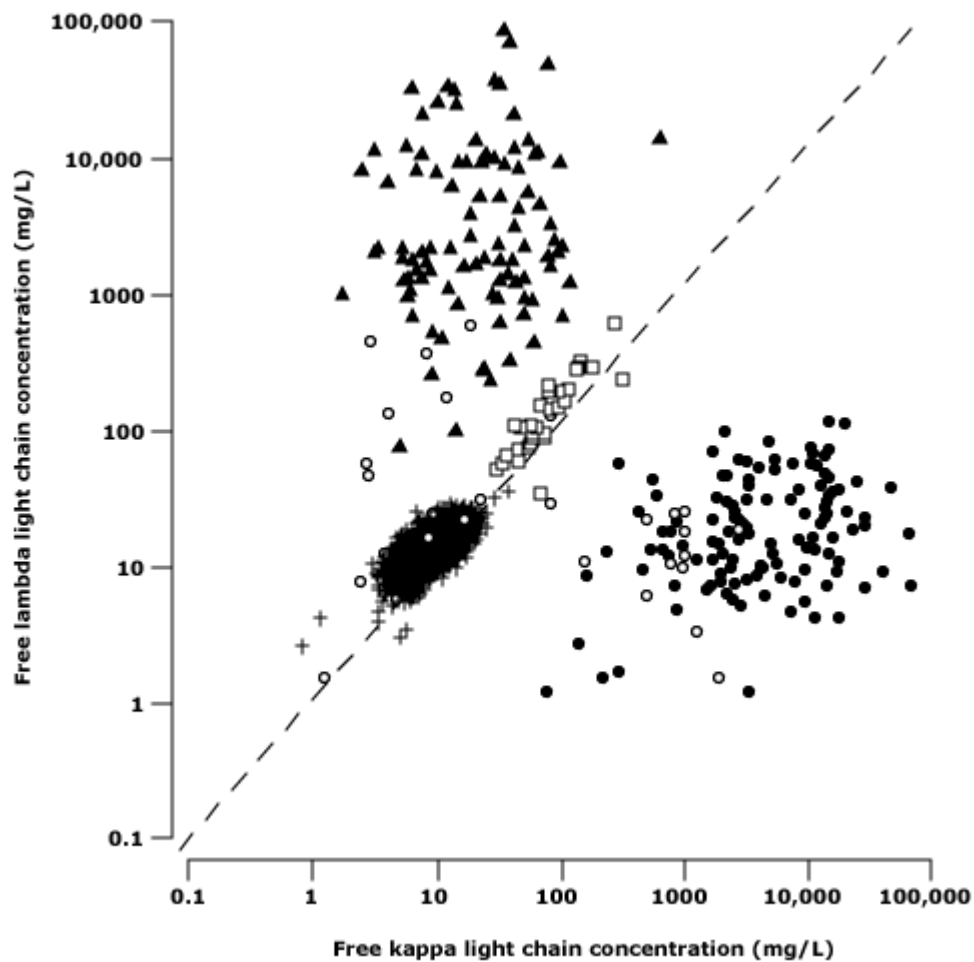
This figure illustrates the immunofixation pattern of a single serum specimen with antisera to heavy chain determinants of IgA, IgG, and IgM, and to kappa and lambda light chain determinants. It shows a discrete IgG band (seen as a dark column) and a discrete lambda band with similar mobility, indicative of the presence of an IgG lambda monoclonal protein. There is also an IgM kappa monoclonal protein.

Triclonal gammopathy



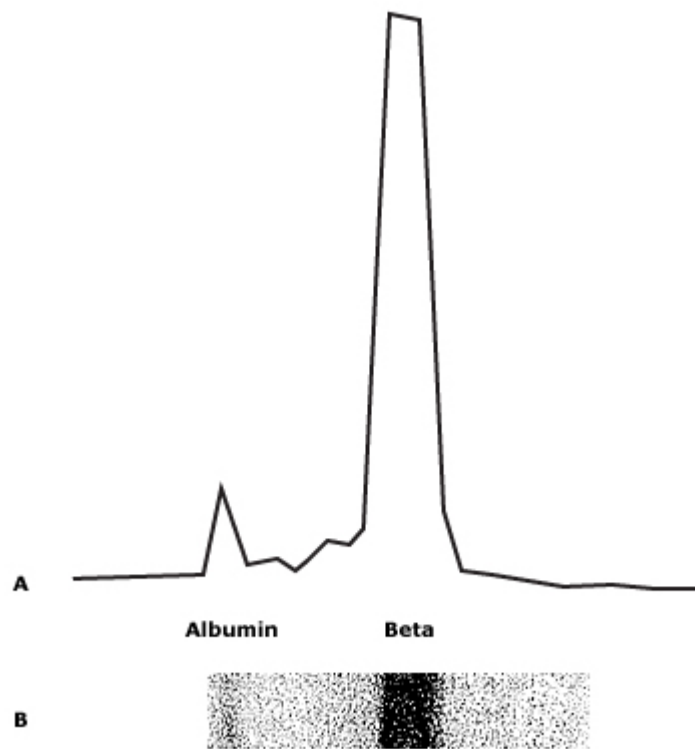
This figure illustrates the immunofixation pattern of a single serum specimen with antisera to heavy chain determinants of IgA, IgG, and IgM, and to kappa and lambda light chain determinants. It shows a discrete IgG band and a discrete kappa band with similar mobility, indicative of an IgG kappa monoclonal protein. There are also IgA lambda and IgM kappa monoclonal proteins.

Serum free light chains



This figure shows simultaneous measurements of free serum kappa (horizontal axis) and lambda (vertical axis) light chains. The dashed line indicates a 1:1 kappa/lambda ratio (weight basis). Results are shown for 282 normal subjects (+), 120 patients with kappa light chain myeloma (closed circles), 140 patients with lambda light chain myeloma (closed triangles), 31 patients with renal impairment from non light chain disorders (open squares) and 28 subjects with non-secretory myeloma (open circles). Note that monoclonality could be detected in many of the latter group using this technique. *Data from Bradwell, AR, et al. Lancet 2003; 361:489.*

Urinary monoclonal protein



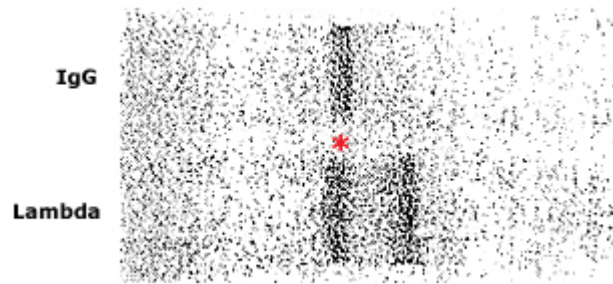
Panel B: This figure illustrates the cellulose acetate electrophoretic pattern of a urine sample. It reveals a dense band of protein with beta mobility. Panel A: Densitometer tracing shows a tall, narrow-based peak of beta mobility. These findings are consistent with a urine monoclonal protein (Bence Jones protein); confirmation of the diagnosis requires demonstration that the protein contains only a lambda or kappa light chain with no heavy chain reactivity.

Urinary monoclonal protein



Immunofixation of a concentrated urine specimen from the previous patient with antisera to kappa and lambda light chains shows a discrete lambda band, indicating a monoclonal lambda light chain (ie, Bence Jones protein of lambda specificity).

Urinary immunoglobulin fragment



This figure illustrates immunofixation of a single urine specimen with antisera to IgG and lambda light chain determinants. There are two lambda bands. A discrete IgG band corresponds to one of the lambda bands (red asterisk). The findings indicate a monoclonal lambda protein plus an IgG lambda fragment.

